Effects of C5 complement inhibitor pexelizumab on outcome in high-risk coronary artery bypass grafting: Combined results from the PRIMO-CABG I and II trials

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Objective: The previous Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery I (PRIMO-CABG I) trial (n = 3099) indicated that C5 complement inhibition with pexelizumab might reduce myocardial infarction (MI) and postoperative mortality. PRIMO-CABG II was designed to investigate the safety and efficacy of terminal complement inhibition in reducing perioperative MI and mortality in patients undergoing CABG surgery who have 2 or more predefined preoperative risk factors.

Methods: PRIMO-CABG II, a randomized, double-blind, placebo-controlled trial, enrolled 4254 patients undergoing CABG with or without valve surgery at 249 hospitals in North America and Western Europe from June 2004 to July 2005. The patients were randomly assigned to receive intravenous pexelizumab or placebo. The primary composite endpoint was the incidence of death or MI within 30 days of randomization.

Results: The PRIMO-CABG II trial did not meet its prespecified primary endpoint of death or MI at 30 days, the secondary endpoints of death at 30 days, or the development of new or worsening congestive heart failure (relative risk 0.91, 0.82, and 1.01, respectively; $P > .05$). However, in a combined analysis of both pivotal trials, PRIMO-CABG I and II (n = 7353), death at 30 days was significantly reduced for the greatest risk subset (n = 2156, pexelizumab 5.7% vs placebo 8.1%, $P = .024$). Furthermore, this mortality reduction persisted throughout the 180-day follow-up period (pexelizumab 11.1% vs placebo 14.4%, $P = .036$).

Conclusions: Pexelizumab was associated with a nonsignificant 6.7% reduction in the primary composite endpoint of death or MI at postoperative day 30 in CABG patients enrolled in the PRIMO-CABG II trial, despite the suggestion of a more favorable treatment effect in the previous PRIMO-CABG I trial. However, an exploratory analysis of the combined PRIMO I and II data set using an established predictive risk model showed a mortality benefit for high-risk surgical patients. (J Thorac Cardiovasc Surg 2011;142:89-98)

During coronary artery bypass graft (CABG) surgery requiring cardiopulmonary bypass (CPB), a systemic inflammatory response is initiated that causes cellular injury and multisystem organ dysfunction.[1] Perioperative complement activation contributes to systemic inflammation and cardiac injury by way of 2 products of C5 cleavage: C5a, a potent anaphylatoxin,[2] and C5b-9, the membrane attack complex that causes cell lysis.[3,4] Pexelizumab is a humanized, single-chain, monoclonal antibody fragment that binds to the C5 component of complement with high affinity, thereby ameliorating acute inflammatory reactions and the associated organ dysfunction.[5]

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The PRIMO-CABG II Steering Committee, Alexion Pharmaceuticals, and Procter & Gamble Pharmaceuticals designed the study, developed the protocol, and determined a statistical analysis plan by consensus. Procter & Gamble Pharmaceuticals and Alexion Pharmaceuticals also provided the study drug and placebo and hired a contract research organization to collect the data from the study sites. Data were collected using electronic case report forms managed by Quintiles and Procter & Gamble, who housed the blinded trial database. The data analyses were initially conducted at Procter & Gamble, and the results and raw data for PRIMO-CABG II, PRIMO-CABG and Phase II-CABG were then given to Dr Smith and the PRIMO-CABG Steering Committee. The final decision on the content of the report rested with the corresponding author in consultation with the other investigators. No formal approval of the manuscript from Procter & Gamble and Alexion occurred; however, Alexion and Procter & Gamble authors contributed to writing the report.

The PRIMO CABG II trial is registered at ClinicalTrials.gov at the following Web address: http://clinicaltrials.gov/ct2/show/NCT00088179.

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Abbreviations and Acronyms

CABG = coronary artery bypass graft
CHF = congestive heart failure
CPB = cardiopulmonary bypass
MI = myocardial infarction
PRIMO = Pexelizumab for Reduction of Infarction and Mortality
RR = relative risk
STS = Society of Thoracic Surgeons

A previous study (Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery [PRIMO-CABG] I) reported that pexelizumab treatment was associated with a statistically significant reduction in myocardial infarction (MI) or death (11.5% vs 14% for placebo, $P = .030$) 30 days after surgery in 3099 patients who had undergone CABG surgery with or without valve surgery.[6] The difference between groups did not reach statistical significance for the primary composite endpoint of death or MI through 30 days for subpopulation of patients undergoing CABG surgery without valve replacement (n = 2746).[6] Enrollment in the PRIMO-CABG I trial required the presence of 1 or more predefined patient risk factors, including female gender, recent or multiple MIs, urgent surgery, previous CABG surgery, a history of diabetes mellitus, and advanced age.[7-9] These risk factors have been demonstrated to predict increased morbidity and mortality after CABG[7] and are becoming increasingly prevalent.[10] A post hoc analysis in the PRIMO-CABG I trial suggested that pexelizumab was effective in reducing death or MI, compared with placebo, in patients with 2 or more of these predefined risk factors.[11] In addition, a parallel reduction was found in perioperative MI in the pexelizumab-treated patients that suggested a biologic mechanism for the associated mortality reduction. This association was further suggested by the protective effects of pexelizumab in surgical patients undergoing a prolonged aortic crossclamp time (>90 minutes)[12] and in randomized, placebo-controlled studies demonstrating a significant mortality reduction in ambulatory patients with acute MI.[13]

On the basis of these observations, the present PRIMO-CABG II trial was designed to confirm the efficacy and safety of pexelizumab in higher risk patients undergoing CABG surgery requiring CPB. The enrollment criteria were changed to require the presence of 2 or more predefined risk factors. The pexelizumab dosing, exclusion criteria, and outcome definitions were otherwise identical to those used in the PRIMO-CABG I trial, with the intention of enabling analysis of the treatment effect in both trials.

MATERIALS AND METHODS

Patients

The PRIMO-CABG II trial was conducted at 249 sites in 7 North American and Western European countries. Patients were eligible for enrollment if they were scheduled for CABG requiring CPB with or without concurrent valve surgery and had 2 or more of the following preoperative baseline risk factors: urgent intervention defined according to the American College of Cardiology/American Heart Association guidelines[9] as requiring hospitalization because of medical factors but able to proceed with surgery within a normal scheduling routine; diabetes mellitus; female gender; previous CABG; a history of a neurologic event (cerebrovascular accident, transient ischemic attack, or carotid endarterectomy); a history of congestive heart failure (CHF) (New York Heart Association class III or IV); or a history of 2 or more MIs (excluding patients who had had an MI within 48 hours before CABG) or of a recent MI that occurred at least 48 hours, but no more than 4 weeks, before CABG surgery. The exclusion criteria included salvage intervention as defined by the American College of Cardiology/American Heart Association guidelines (on-going cardiopulmonary resuscitation enroute to the operating room)[9]; current cardiogenic shock, acute left ventricular rupture, acute ventricular septal rupture, or acute papillary muscle rupture; active infection that the investigator considered clinically significant; known or suspected hereditary complement deficiency; current or previous participation in any other investigational drug study or exposure to any investigational drug or device within the previous 30 days; and pregnancy or lactation. The institutional review boards, or equivalent, at each site approved the protocol, and all patients provided written informed consent. Of those eligible for enrollment, 53% were randomized.

Study Treatment

The patients were randomized in a double-blind fashion using a central telephone-based system to receive either an intravenous pexelizumab bolus (2.0 mg/kg) followed by a 24-hour infusion (0.05 mg/kg/h), or placebo bolus and infusion.[5] The bolus was administered as soon as possible after general anesthesia induction, but not later than 10 minutes before CPB. The dosing regimen was the same as that used in the PRIMO-CABG I trial, in which profound complement inhibition was demonstrated.[6] Stratification occurred within each site according to the type of surgery planned and the reoperative status of the patient. The operative techniques and perioperative management were as clinically indicated at each site, with enrollment predicated on the intended use of CPB with mild to moderate hypothermia.

Definition of Events

Death, defined as all-cause mortality, was assessed through postoperative day 180. MI was defined as a peak creatine kinase-MB of at least 100 ng/mL by postoperative day 4, independent of Q-wave evidence; a creatine kinase-MB of at least 70 ng/mL by postoperative day 4 with Q-wave evidence of an MI; new Q-wave evidence of MI by postoperative day 30 that was not present by day 4; MI (with or without Q-wave evidence) identified by the investigator and confirmed by a Clinical Events Committee by day 30. All MIs were adjudicated by this committee, which remained unaware of the study treatment. Serum samples were collected at 4, 8, 12, 16, 24, 36, 48, 72, and 96 hours postoperatively for subsequent CK-MB analysis at a central core laboratory. Electrocardiograms were recorded on patient enrollment and at 2, 4, and 30 days postoperatively and were interpreted at a central laboratory whose personnel were unaware of the treatment assignment.

Study Endpoints

The prespecified primary endpoint was defined as the incidence of a composite of death (all causes) or MI (death/MI) through day 30 in patients undergoing CABG surgery with or without concomitant valve surgery. The secondary endpoints included the incidence of death through day 30 and day 90, the incidence of new or worsening CHF during the index

hospitalization, or rehospitalization for CHF through day 30. The presence of new or worsening CHF was determined by a Clinical Events Committee, who were unaware of the treatment arm. The tertiary endpoints included death at day 180, worsening of the New York Heart Association score from baseline to day 30, and resource use (eg, length of hospital stay, interval in intensive care) through day 180.

Safety

The patients were monitored for adverse events while hospitalized and at the postoperative day 30 clinic visit. Adverse events were collected using a cardiac events checklist (completed at days 30, 90, and 180) and a postoperative infection checklist (completed at days 30, 90, and 180). The checklists contained prespecified cardiac- or infection-related adverse events typically reported by CABG surgery patients and were intended to simplify and standardize the collection of these events.

Statistical Analysis

A sample size of 2000 patients per treatment group was required to provide 90% power to detect a treatment difference between an anticipated 16% placebo group event rate for the primary endpoint and an anticipated 12% active treatment group event rate using a 2-sided, χ^2 test and $\alpha = .05$.

The primary efficacy analysis was performed on the binary composite endpoint (death or MI through day 30) for all randomized patients (the intent-to-treat population). A comparison of the incidence rates between the treatment groups was performed using χ^2 testing with stratification according to the type of surgery (CABG with or without valve surgery, mitral or other valve surgery, first or repeat CABG). The sensitivity analysis of the day 30 composite endpoint included an analysis of each component, as well as an analysis of the day 4 composite endpoint and each of its components. Survival analysis was performed on the mortality data and included Kaplan-Meier curve estimation and Cox proportional hazard modeling. The log-rank test was used to test the difference in the time-to-event between the 2 treatment groups. The consistency of the treatment effect was evaluated using subgroup analyses based on a number of characteristics (eg, predetermined risk factors, age, sex, race, preoperative medications, intraoperative blood-sparing agents, and other surgical conduct variables). Other endpoints were analyzed using nonparametric rank analysis (continuous endpoints) and stratified χ^2 testing (binary endpoints).

A secondary analysis was performed in which the predefined risk factors were weighted using mapped coefficients derived in the Society of Thoracic Surgeons (STS) National Database mortality risk algorithm[7] to create a single mortality risk probability for each patient (post hoc). Missing risk factor coefficients were imputed to the STS national mean (2004 data harvest) for continuous variables, to the lowest risk for categorical variables, and to the gender-specific mean for body surface area. The baseline characteristics were summarized by treatment group and assessed for differences between treatment groups using a t test (continuous variables) or χ^2 test (for categorical variables).

Data from the PRIMO-CABG II trial (n = 4254) were analyzed individually and then pooled with data from the PRIMO-CABG I trial (n = 3099) for subsequent analysis. STS predictive algorithms for mortality could be applied to 95% of the 7353 patients. The STS predictive algorithms were not assignable to patients with more than 1 valve operation or in patients who did not undergo CABG. The data collection forms, data definitions, and drug infusion protocols were identical for the 2 pivotal trials. Statistical Analysis Systems, version 8.2, and S-Plus, version 2000 (SAS Institute, Cary, NC), were used for all statistical analyses.

RESULTS OF PRIMO-CABG II TRIAL

Patient Characteristics and Disposition

A total of 4254 patients undergoing CABG with or without valve surgery were randomized and complete data collected for all but 37 who were lost to follow-up (Figure 1). The baseline characteristics were similar in the 2 treatment groups (Table 1).

Efficacy

Pexelizumab was associated with a nonsignificant 6.7% reduction in the primary composite endpoint, death or MI, compared with placebo (15.2% [323/2130] vs 16.3 % [341/2098], $P = .20$) (Table 2). The incidence of perioperative MI through day 30 (relative risk [RR] 0.93, $P = .31$), death at 30 days (RR 0.82, $P = 0.18$), and death at 90 days (RR 0.92, $P = .51$) were also reduced insignificantly. The development of new or worsening CHF (RR 1.01, $P = .93$) was unaffected by pexelizumab. The duration of aortic cross-clamping did not appear to differentially influence the incidence of the primary endpoint of 30-day death or MI when pexelizumab was administered rather than placebo.

Association of Efficacy With Predetermined Risk Factors

Insignificant trends were noted associating pexelizumab treatment with reduced mortality for each of the predetermined risk factors, except for previous MI. Pexelizumab efficacy was not increased with an increasing number of risk factors per patient (Table 3). The prespecified subgroup analysis, with the patients stratified by type of cardiac surgery, showed similar nonsignificant trends of a pexelizumab reduction of the primary composite endpoint (Table 4).

Safety

The number and proportion of patients experiencing adverse events was similar in both treatment groups. The incidence of allergic reactions was similar in the 2 treatment groups (placebo 0.2%; pexelizumab 0.7%). The most frequent adverse events in both groups were atrial fibrillation, conduction disorders, and clinical CHF. No clinically important differences were seen between the 2 groups in the adverse or cardiac adverse event profiles. Also, the infection logs showed no differences in overall infection at 30, 60, and 90 days after the procedure (placebo 22.7%, 26.6%, and 28.0% vs pexelizumab 22.2%, 26.4%, and 27.9%, respectively). No meaningful or consistent differences were seen between the 2 treatment groups in the incidence or types of postoperative infection, except for a significant reduction in the prevalence of postoperative sepsis (4.5% through 180 days for placebo vs 3.0% for pexelizumab in the PRIMO-CABG II trial; RR 0.66, 95% CI 0.48 to 0.91; $P = .01$. This effect was also significant in the PRIMO-CABG I and II combined randomized database (4.0% for placebo vs 2.6% for pexelizumab).

EXPLORATORY ANALYSIS AND COMBINED RESULTS OF PRIMO-CABG I AND II TRIALS

Extensive analysis was performed to understand the inability of the PRIMO-CABG II trial to replicate the findings

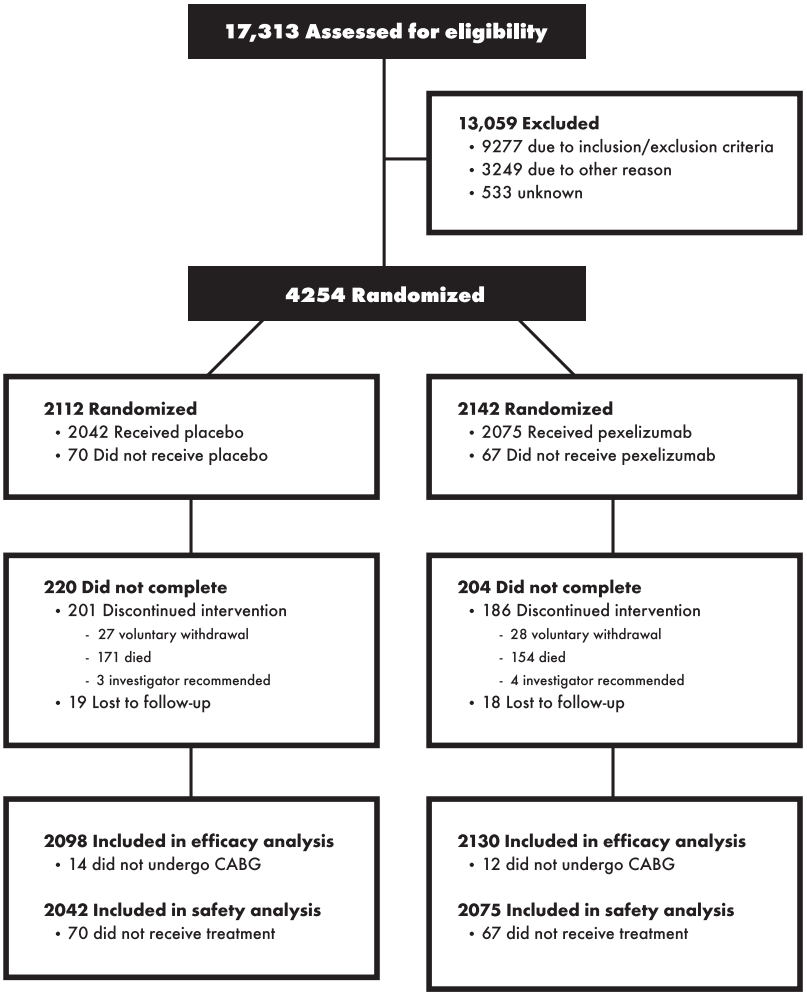

FIGURE 1. Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery *(PRIMO-CABG)* II patient flow diagram.

in the higher risk subset of the PRIMO-CABG I trial and to provide a comprehensive analysis of all randomized CABG patients to place any potential role for pexelizumab in perspective. A review of the samples of the study drug indicated that the expected potency of the treatment agent was present.

Comparison of PRIMO-CABG II to PRIMO-CABG I Trials

Substantial baseline differences were seen in the patients enrolled in the 2 trials. By design, the incidence of predefined risk factors and the number of risk factors per patient was greater in the PRIMO-CABG II than in the PRIMO-CABG I patients (Table 5). The most striking and unanticipated difference was that PRIMO-CABG II patients compared with PRIMO-CABG I patients were treated more frequently with preoperative statins (76.4% vs 22.9%) and with intraoperative aprotinin (50.0% vs 25.1%). The use of aprotinin was associated with an increased prevalence of surgical risk and the number of risk factors; however, the relative mortality reduction afforded by pexelizumab was unaffected by either aprotinin or statin use (data not shown).

Prespecified Outcome Analysis of Merged PRIMO-CABG II and I Database

Analysis of the PRIMO-CABG II trial data merged with the PRIMO-CABG I trial data (n = 7353) showed that the composite endpoint of death or MI at 30 days was significantly reduced, occurring in 501/3679 pexelizumab-treated patients compared with 556/3637 placebo-treated patients (RR 0.88, 95% CI 0.79 to 0.98; $P = .0198$). The secondary endpoint of all-cause death was insignificantly reduced, however, with a RR of 0.79 at 30 days ($P = .054$), 0.87 at 90 days ($P = .134$), and 0.86 at 180 days ($P = .074$).

Analysis of Predefined Risk Factors and Their Relationship to Predicted Surgical Risk

The enrollment design of the PRIMO-CABG II trial was based on the favorable effect of pexelizumab seen in the high-risk subset of the PRIMO-CABG I patients who had

TABLE 1. PRIMO-CABG II: baseline demographic and anthropometric characteristics (all randomized patients)

Characteristics	Placebo (n = 2112)	Pexelizumab (n = 2142)	*P* value
Age (y)*	66.2 (35–90)	66.2 (31–91)	.80
Left ventricular ejection fraction*	50.4 (49.7–51.0)	50.5 (49.8–51.1)	.85
Predicted mortality*	0.028 (0.026–0.029)	0.028 (0.026–0.030)	.63
Diabetes mellitus	1246 (59.0)	1298 (60.6)	.29
Urgent surgery	1534 (72.6)	1517 (70.8)	.19
Previous CABG	199 (9.4)	228 (10.6)	.18
History of heart failure	843 (40.0)	838 (39.1)	.60
History of neurologic event	485 (23.0)	506 (23.6)	.61
Female sex	852 (40.3)	839 (39.2)	.29
Preoperative statin	1609 (76.2)	1639 (76.5)	.97
Aprotinin	1020 (48.3)	1085 (50.7)	.12
Investigator country			.99
Canada	73 (3.5)	70 (3.3)	
Germany	374 (17.7)	374 (17.5)	
France	125 (5.9)	127 (5.9)	
United Kingdom	34 (1.6)	31 (1.4)	
The Netherlands	84 (4.0)	92 (4.3)	
United States of America	1422 (67.3)	1448 (67.6)	

Data are presented as n (%), unless otherwise specified. *Data are presented as mean (95% confidence interval). *P* values for age are from *t* test, *P* value for sex from Fisher's exact test; and *P* value for investigator country from χ^2 test. *PRIMO-CABG,* Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery; *CABG,* coronary artery bypass graft.

had 2 or more predefined risk factors. The prospective use of the number of risk factors, rather than the number and predictive value of each risk factor, as an inclusion criterion, resulted in enrollment in the PRIMO-CABG II trial of a significant number of patients who actually had a low predicted risk.

To better characterize the relationship between the preoperative risk and the pexelizumab effect, the predicted operative mortality was calculated for each patient using the STS mortality risk coefficients for CABG and CABG/valve surgery to weigh their relative contribution to mortality risk. Overall, the mean PRIMO-CABG II trial predicted operative mortality rate was 2.8%, significantly greater than the 2.1% rate calculated for the PRIMO-CABG I trial.

The mean predicted risk of PRIMO-CABG I patients was 2% for the subset with 2 predefined risk factors (the minimum entry criterion for PRIMO-CABG II). On average, PRIMO-CABG II patients included more patients with multiple risk factors and more patients with a predicted risk greater than 2% than were enrolled in the PRIMO-CABG

TABLE 2. PRIMO-CABG II: effect of pexelizumab treatment on all-cause mortality and myocardial infarction

	Placebo (n = 2112)		Pexelizumab (n = 2142)			
Endpoints	n	Denominator (%)	n	Denominator (%)	RR (95% CI)	*P* value
Days 0–4						
Composite	279	2103 (13.3)	280	2135 (13.1)	0.96 (0.83–1.12)	.65
Death	36	2103 (1.7)	40	2135 (1.9)	1.10 (0.69–1.75)	.77
MI	258	2112 (12.2)	251	2142 (11.7)	0.93 (0.80–1.09)	.39
Non–Q-wave infarction	219	2112 (10.4)	196	2142 (9.2)	0.86 (0.72–1.02)	.09
Q-wave infarction	39	2112 (1.9)	55	2142 (2.6)	1.25 (0.83–1.90)	.14
Days 0–30						
Composite	341	2098 (16.3)	323	2130 (15.2)	0.91 (0.80–1.05)	.20
Death	96	2098 (4.6)	81	2130 (3.8)	0.82 (0.61–1.10)	.18
MI	280	2112 (13.3)	269	2142 (12.6)	0.93 (0.79–1.08)	.31
Non–Q-wave infarction	225	2112 (10.7)	200	2142 (9.3)	0.85 (0.71–1.02)	.08
Q-wave infarction	55	2112 (2.6)	69	2142 (3.2)	1.15 (0.81–1.64)	.27
Days 0–90						
Death	135	2083 (6.5)	129	2123 (6.1)	0.92 (0.73–1.17)	.51
Days 0–180						
Death	168	1611 (10.4)	151	1635 (9.2)	0.87 (0.71–1.07)	.20

RR and 95% CI = stratified by (CABG/previous CABG and valve surgery) pexelizumab to placebo ratio. *P* value from Cochran-Mantel-Haenszel test stratified by CABG/previous CABG and valve surgery. *PRIMO-CABG,* Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery; *CABG,* coronary artery bypass graft; *RR,* relative risk; *CI,* confidence interval; *MI,* myocardial infarction.

TABLE 3. PRIMO-CABG II: primary composite endpoint (all-cause mortality or myocardial infarction) through day 30 stratified by baseline risk factors

	Placebo		Pexelizumab			
Baseline group	n (%)	N	n (%)	N	RR (95% CI)	*P* value
Female sex	150 (17.7)	846	134 (16.2)	827	0.91 (0.74–1.13)	.38
Diabetes	182 (14.7)	1238	184 (14.2)	1293	0.93 (0.77–1.12)	.49
CHF	172 (20.5)	839	159 (19.0)	835	0.89 (0.73–1.07)	.34
MI	103 (14.7)	700	99 (15.1)	657	1.03 (0.81–1.32)	.85
Neurologic event	93 (19.3)	482	89 (17.7)	504	0.91 (0.71–1.17)	.44
Urgent intervention	232 (15.3)	1521	208 (13.8)	1507	0.89 (0.75–1.05)	.16
Previous CABG	66 (33.2)	199	76 (33.5)	227	0.98 (0.74–1.29)	.94
>2 Risk factors	338 (16.3)	2077	320 (15.2)	2112	0.91 (0.79–1.04)	.18
>3 Risk factors	213 (19.1)	1116	196 (17.6)	1115	0.90 (0.76–1.07)	.26
>4 Risk factors	86 (20.3)	424	84 (21.2)	397	0.95 (0.73–1.24)	.96

P value is from Cochran-Mantel-Haenszel test stratified by CABG/previous CABG and valve surgery. *N,* Number of patients randomized in treatment group at risk of composite endpoint; *CHF,* congestive heart failure; other abbreviations as in Table 2.

I trial (Figure 2). However, a histogram of the predicted risk frequency for the 2 trials showed the relative similarity of the risk profiles in the PRIMO-CABG I and PRIMO-CABG II trials despite the increased prevalence of multiple risk factors in the latter trial (Figure 3). Only 33% of PRIMO-CABG II patients were subsequently determined to have a predicted risk of 2% or greater, despite the intention to evaluate pexelizumab in a higher risk patient population than that evaluated in the PRIMO-CABG I trial.

Accordingly, the pooled data of the PRIMO-CABG I and II trials were analyzed by dividing the data set into 2 groups, the 2% or greater predicted mortality rate of the 2-risk factor PRIMO-CABG I trial patients or less than 2% (Table 6). The high-risk CABG-only subgroup (22% of the enrolled CABG patients) had a significant 21.8% reduction ($P < .05$) in the prespecified composite endpoint (death or MI through 30 days). A nonsignificant trend in mortality reduction was observed at day 30 (25.5%), day 90 (19.8%) and through day 180 (17.3%). The entire high-risk subgroup, including those undergoing concomitant valve procedures (31% of all enrolled patients), experienced a significant and persistent mortality benefit from pexelizumab treatment compared with placebo. The risk reduction for death or MI through day 30 (P = NS), death at 30 days, death at 90 days (P = NS), and death at 180 days was 12%, 30.3%, 21.5%, and 21.4%, respectively. The patients with a predicted mortality risk of less than 2% had no discernable benefit or additional risk trend with pexelizumab compared with placebo.

The Kaplan-Meier survival curves for all PRIMO-CABG I and PRIMO-CABG II patients and for the high- and low-predicted mortality groups are illustrated in Figure 4. A significant survival advantage ($P = .042$) is shown for pexelizumab-treated patients having an STS predicted mortality of 2% or greater. However, pexelizumab appeared to confer no survival hazard or advantage compared with placebo for low-risk patients, those with an STS predicted mortality rate of less than 2%.

The STS National Adult Cardiac Database reported on 281,347 CABG or CABG/valve procedures from January 2005 to June 2006, with the finding that 35.9% of the CABG patients and 45% of all the patients would have met the 2% predicted mortality threshold for pexelizumab effectiveness.[14] Thus, despite the intention to enroll high-risk patients, both pivotal trials enrolled patients with a lower risk profile than typically seen in clinical practice.

DISCUSSION

Effectiveness of Pexelizumab for All Enrolled Patients

Although the data from the PRIMO-CABG II trial reconfirmed the previously established safety of administering

TABLE 4. PRIMO-CABG II: primary composite endpoint (all-cause mortality or myocardial infarction) through day 30 by randomized stratum

	Placebo		Pexelizumab			
Baseline group	n (%)	N	n (%)	N	RR (95% CI)	*P* value
Primary CABG	275 (14.5)	1899	247 (12.98)	1903	0.89 (0.76–1.04)	.17
Previous CABG	66 (33.2)	199	76 (33.48)	227	0.98 (0.74–1.29)	.94
CABG plus valve surgery	94 (28.8)	326	95 (27.86)	341	0.92 (0.72–1.18)	.54
CABG only	247 (13.9)	1772	228 (12.74)	1789	0.91 (0.77–1.07)	.26
Nonmitral valve surgery	58 (27.2)	213	51 (24.88)	205	0.90 (0.66–1.23)	.43
Mitral valve surgery	36 (31.9)	113	44 (32.35)	136	0.96 (0.66–1.41)	.98

P value is from Cochran-Mantel-Haenszel test stratified by CABG/previous CABG and valve surgery. *N,* Number of patients randomized in treatment group at risk of composite endpoint; other abbreviations as in Table 2.

TABLE 5. Comparative preoperative patient characteristics

Variable	PRIMO-CABG I (n = 3099) (%)	PRIMO-CABG II (n = 4254) (%)
Previous CABG	8.4	10.0
History of CHF	30.5	39.5
CABG plus valve procedure	11.8	16.3
Previous neurologic event	14.3	23.3
Female sex	26.8	39.5
History of MI	11.3	54.8
Diabetes	41.0	59.8
≥ 2 Previous MIs	20.3	32.0
Urgent surgery	63.7	71.7
1 Risk factor	37.6	7.5
2 Risk factors	36.2	47.9
3 Risk factors	18.7	30.7
4 Risk factors	5.0	12.0
5 Risk factors	0.9	1.8
6 Risk factors	0.0	0.1
Preoperative statin use	22.9	76.4
Aprotinin use	25.1	50.0

CHF, Congestive heart failure; other abbreviations as in Table 2.

a C5 terminal complement inhibitor,[6] its efficacy could not be conclusively demonstrated. The previously reported relationship between the predefined patient risk factors and treatment effect was not demonstrable in the PRIMO-CABG II trial. The PRIMO-CABG II trial was designed to enroll patients with greater prospective risk and, therefore, to enrich the population studied with patients who showed a positive treatment effect for MI reduction and an associated mortality reduction in the previously executed PRIMO-CABG I trial. However, because the trial was not powered to demonstrate an independent mortality reduction, the absence of a robust treatment effect on MI resulted in failure to significantly affect the composite endpoint.

When all the randomized patients from the PRIMO-CABG I and II trials (n = 7353) were considered, a statistically significant reduction was seen in the primary composite endpoint of death or MI at 30 days; however, the efficacy trend for mortality alone remained insignificant through postoperative day 180 (risk reduction 14%, $P = .074$). The mechanism of mortality reduction in cardiac surgery patients was not clarified by the results from the PRIMO-CABG II trial. The absence of a significant favorable treatment effect of pexelizumab on reducing myocardial damage was consistent with the results of the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX) trial,[15] which showed no benefit of pexelizumab in patients with acute MI treated with percutaneous intervention. Furthermore, the reported relationship between prolonged induced cardiac ischemia and treatment effect[12] was also not demonstrable.

Study Limitations

The most striking differences between the PRIMO-CABG II study population and the previously studied patients in the PRIMO-CABG I trial were the increased enrollment of very high-risk patients and the increased use of aprotinin and statins. Both aprotinin and statins have powerful anti-inflammatory effects,[16-18] which might have

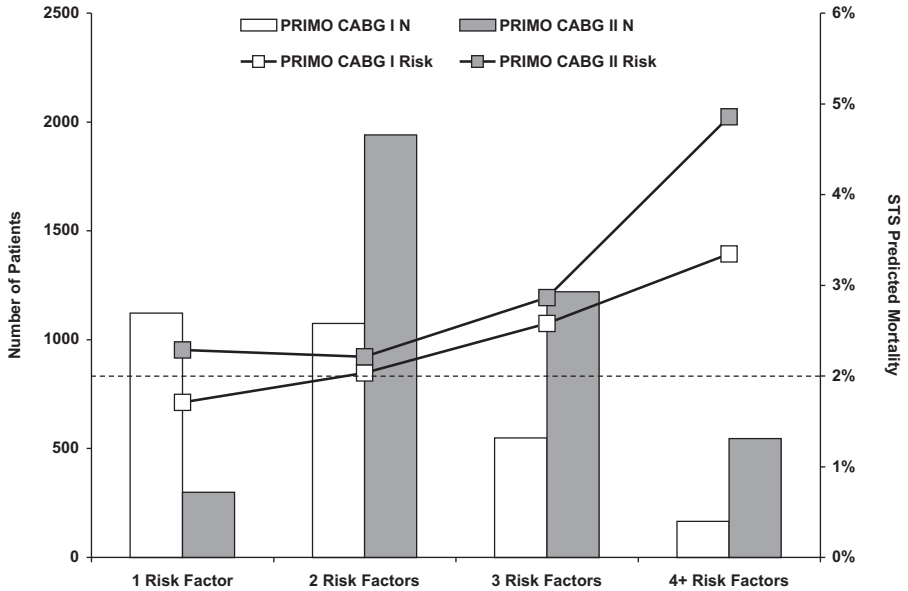

FIGURE 2. Enrollment characterized by number of risk factors and Society of Thoracic Surgeons-predicted mortality risk is illustrated for Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery *(PRIMO-CABG)* I and II trials. Percentage of enrollment by number of risk factors shown in *light bars* for PRIMO-CABG I and *dark bars* for PRIMO-CABG II. Society of Thoracic Surgeons *(STS)* predicted mortality risk for each risk factor group shown as *light line* and *point estimate* for PRIMO-CABG I and *dark line* and *point estimate* for PRIMO-CABG II. Reference line at 2% predicted mortality risk is calculated risk equivalent for 2 or more risk factors for PRIMO-CABG I.

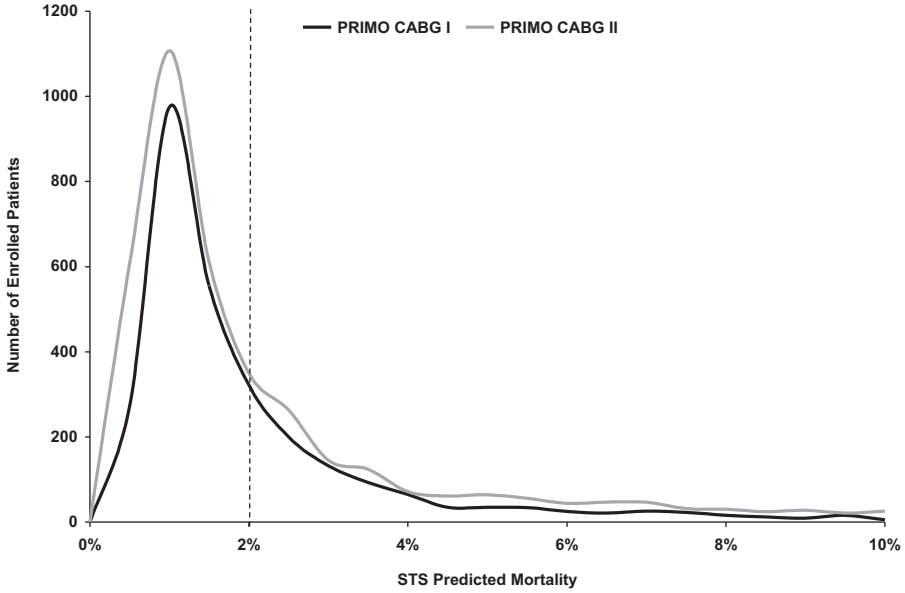

FIGURE 3. Histogram of number of enrolled patients in Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery *(PRIMO-CABG)* I *(gray line)* compared with PRIMO-CABG II *(black line).* Calculated average intended enrollment threshold for PRIMO-CABG II *(vertical line)* placed at 2% predicted mortality.

reduced the adverse effect of the systemic inflammatory response generated during CPB and cardiac surgery.[19]

The increased use of these agents might, therefore, have blunted the efficacy of pexelizumab. Aprotinin, in particular, was administered more frequently in the higher risk subset of the PRIMO-CABG II patients, for whom the pexelizumab effect was expected to be greater. Compared with the PRIMO-CABG I trial, in which the relationship between risk and

TABLE 6. PRIMO-CABG I and II risk reduction by predicted mortality in patients receiving CABG and all patients

	CABG only		All patients	
	STS predicted mortality		STS predicted mortality	
	< 2%	≥ 2%	< 2%	≥ 2%
Patients (n)	4687	1340	4804	2156
%	78%	22%	69%	31%
Death or MI through day 30				
Pexelizumab	9.66%	14.88%	9.6%	19.9%
Placebo	10.41%	19.04%	10.3%	22.6%
Risk reduction	–7.2%	–21.8%	–6.9%	–12.0%
P value	.41	.049	.41	.12
Death through 30 days				
Pexelizumab	2.03%	5.52%	2.0%	5.7%
Placebo	1.95%	7.41%	1.9%	8.1%
Risk reduction	4.1%	–25.5%	3.1%	–30.3%
P value	.92	.18	.87	.024
Death through 90 days				
Pexelizumab	2.71%	8.78%	2.7%	9.0%
Placebo	2.61%	10.95%	2.6%	11.5%
Risk reduction	3.8%	–19.8%	6.7%	–21.5%
P value	.86	.20	.72	.06
Death through 180 days				
Pexelizumab	3.28%	11.02%	3.3%	11.1%
Placebo	3.32%	13.32%	3.3%	14.1%
Risk reduction	–1.2%	–17.3%	0.6%	–21.4%
P value	1	.21	.96	.036

STS, Society of Thoracic Surgeons; other abbreviations as in Table 2.

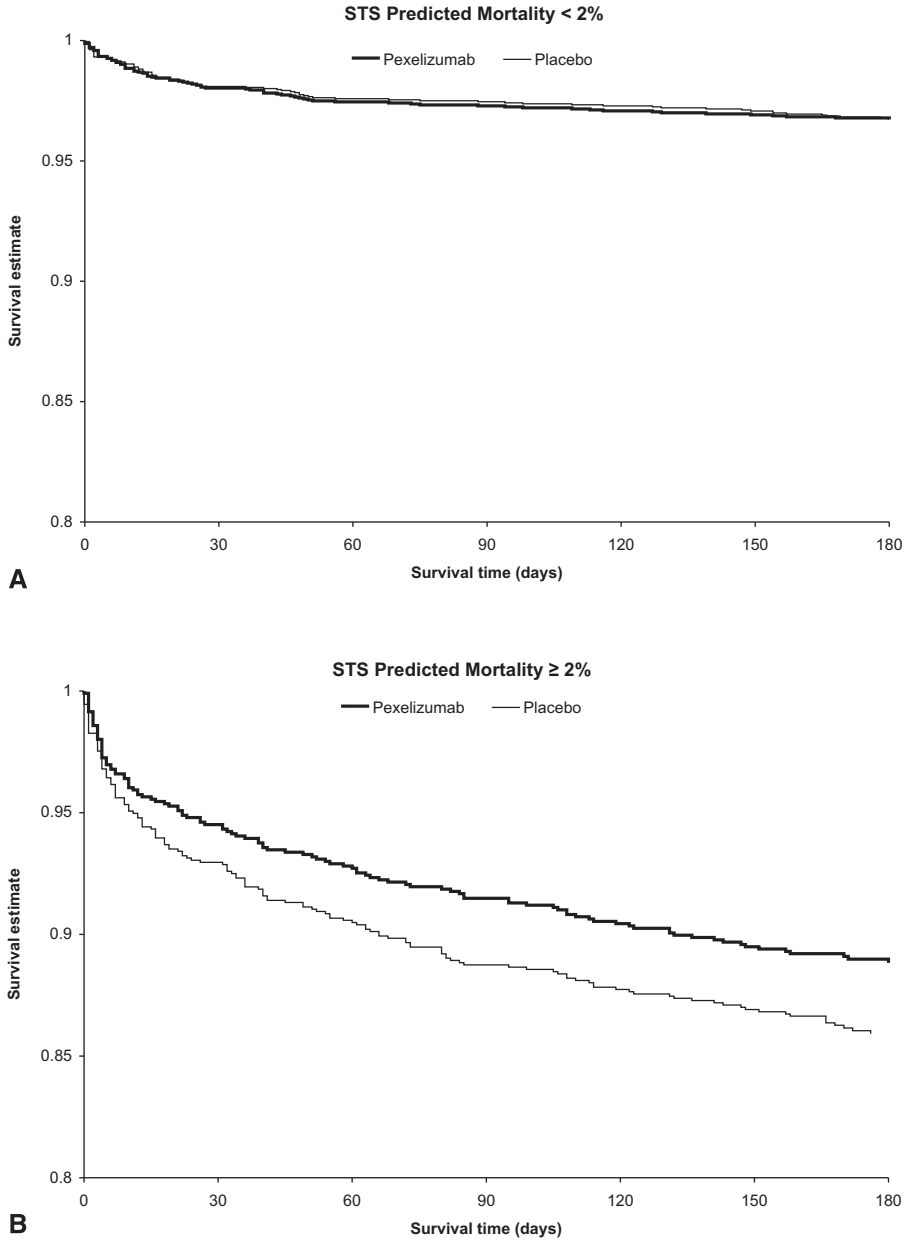

FIGURE 4. Kaplan-Meier survival curves illustrated for combined patients enrolled in Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery *(PRIMO-CABG)* I and II stratified by predicted mortality risk. (A) Survival in patients with predicted mortality <2% with pexelizumab treatment *(dark line)* compared with placebo *(gray line).* (B) Survival in patients with predicted mortality of 2% or greater with pexelizumab treatment *(dark line)* compared with placebo *(gray line).*

pexelizumab effect was demonstrated, aprotinin was used almost twice as frequently and might have reduced the ability to identify the true treatment effect of pexelizumab. The mechanism of this interaction has yet to be identified.

As with all clinical trials, the ability to generalize these results was limited by the selective trial enrollment and a changing treatment environment. This was particularly true for this trial, in which aprotinin is no longer available and virtually all patients are now treated with statins before and after surgical intervention.

Effectiveness of Pexelizumab for High-Risk CABG and CABG/Valve Patients

Pexelizumab appears to be safe and effective in reducing mortality for high-risk CABG and CABG/valve patients. When the patients were stratified according to a validated predicted mortality risk using the STS National database algorithm, those with a predicted risk of 2% or more experienced a significant reduction in mortality that persisted through 180 days. The STS National Cardiac Database has indicated that in contemporaneous U.S. practice, 45% of patients meet this

threshold criterion. Thus, the mortality reduction afforded through pexelizumab use could be substantial.

CONCLUSIONS

The previously identified efficacy of pexelizumab in reducing perioperative MI and its increased effectiveness during prolonged surgically induced ischemia were not apparent in the PRIMO-CABG II trial. Although not meeting its primary endpoint, which was a composite variable of death or MI, the results of the present trial were consistent with previous investigations that suggested that pexelizumab reduces mortality in patients undergoing CABG surgery through its complement inhibiting properties in properly selected patients. This favorable treatment effect was significant in the highest risk patients, including those with preoperative characteristics associated with a predicted mortality rate of 2% or more. These patients account for an estimated 45% of all CABG and CABG/valve surgery performed in the United States.

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